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PATENT & TRADEMARK OFFICE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Eugene D. THORSETT, *et al.*

Title: CARBAMYLOXY COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

Appl. No.: 09/987,619

Filing Date: November 15, 2001

Examiner: D. Lukton

Art Unit: 1653

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Kristen Cumming (Signature)

AMENDMENT AND REPLY UNDER 37 CFR 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply and Amendment is in response to the Office Action (Paper No. 200040401) mailed April 23, 2004 for the above-noted application. The extendable deadline for filing a response is July 23, 2004. Accordingly, this response is timely filed. Entry and consideration of the following amendments and response is requested.

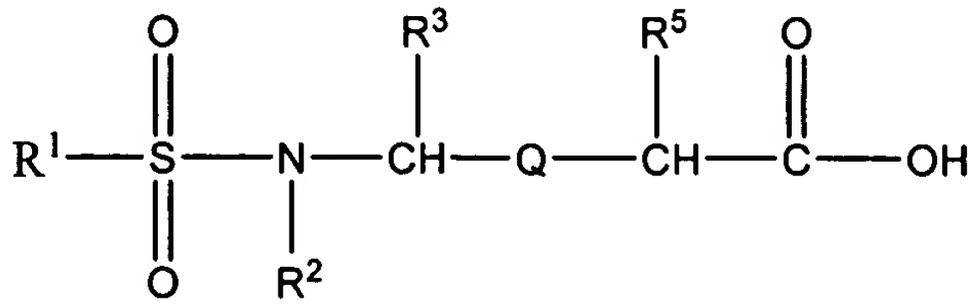
AMENDMENTS

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (previously presented): A compound of formula I:



(I)

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -0-Z-$NR^8R^{8'}$ and -0-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

$-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

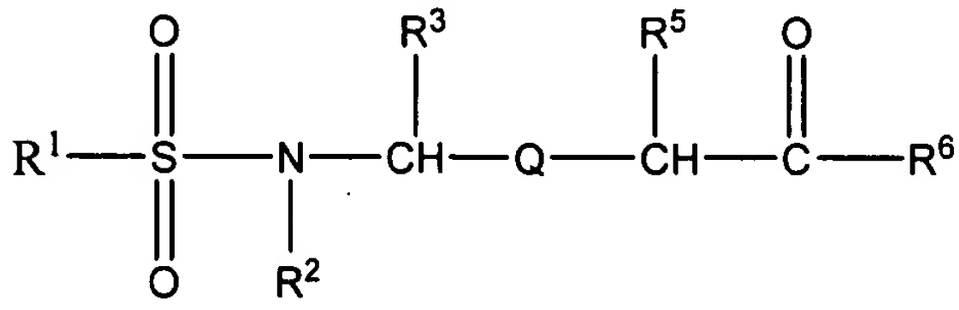
x is an integer of from 1 to 4;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Claims 2–34 (cancelled).

Claim 35 (previously presented): A compound of formula IA:



(IA)

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted allcyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic;

R^5 is -(CH$_2$)$_x$-Ar-R$^{5'}$ and R$^{5'}$ is selected from the group consisting of -O-Z-NR^8 R$^{8'}$ and -O-Z-R^{12} wherein R^8 and R$^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl,

heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and

$-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Claim 36 (previously presented): A compound according to Claims 1 or 35 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl.

Claim 37 (previously presented): A compound according to Claims 1 or 35 wherein R^1 is selected from the group consisting of methyl, isopropyl, *n*-butyl, benzyl, phenethyl, phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-

fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-t-butoxyphenyl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, 2- carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-)phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-($CH_3SC(=NH)$-)phenyl, 4-chloro-3 -($H_2NS(O)_2$-)phenyl, 1-naphthyl, 2-naphthyl, pyridin-2-yl, pyridin-3-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)- l,2,3,4-tetrahydroisoquinolin-7-yl, morpholin-4-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methylimidazol-4-yl, 1 -N-methylpyrazol-3-yl, 1 -N-methylpyrazol-4-yl, 1-N-butylpyrazol-4-yl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, l-N-methyl-5-methyl-3-chloropyrazol-4-yl, 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

Claim 38 (previously presented): A compound according to Claims 1 or 35 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-Φ.

Claim 39 (previously presented): A compound according to Claims 1 or 35 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylrnethyl, -CH_2CH_2-COOH, -CH_2-COOH, 2-amidoethyl, iso-butyl, t-butyl, -CH_2O-benzyl and hydroxymethyl.

Claim 40 (previously presented): A compound according to Claims 1 or 35 wherein Q is -C(O)NH- or -C(S)NH-.

Claim 41 (previously presented): A compound according to Claims 1 or 35 wherein Ar is aryl or substituted aryl.

Claim 42 (previously presented): A compound according to Claim 41 wherein Ar is phenyl or substituted phenyl and *x* is 1.

Claim 43 (previously presented): A compound according to Claim 1 or 35 wherein R^5 is selected from the group consisting of

3-[$(CH_3)_2NC(O)O$-] benzyl,

4-[($CH_3)_2NC(O)O$-]benzyl,

4-[($CH_3)_2NS(O)_2O$-] benzyl,

4-[(piperidin- 1'-yl)C(O)O-] benzyl,

4-[(piperidin-4'-yl)C(O)O-]benzyl,

4-[(1'-methylpiperidin-4'-yl)C(O)O-]benzyl,

4-[(4'-hydroxypiperidin-1'-yl)C(O)O-]benzyl,

4-[(4'-formyloxypiperidin-l'-yl)C(O)O-]benzyl,

4-[(4'-ethoxycarbonylpiperidin- 1-yl)C(O)O-]benzyl,

4-[(4'-carboxylpiperidin- 1'-yl)C(O)O-]benzyl,

4-[(3 ' -hydroxymethylpiperidin- 1' -yl)C(O)O-]benzyl ,

4-[(4'-hydroxymethylpiperidin- 1'-yl)C(O)O-]benzyl,

4-[(4'-phenyl-1'-Boc-piperidin-4'-y1)-C(O)O-]benzyl,

4-[(4'-piperidon-1'-yl ethylene ketal)C(O)O-]benzyl,

4-[(piperazin-4'-y1)-C(O)O-]benzyl,

4-[(1'-Boc-piperazin-4'-y1)-C(O)O-] benzyl,

4-[(4'-methylpiperazin-1'-yl)C(O)O-]benzyl,

4-[(4'-methylhomopiperazin- 1' -yl)C(O)O-]benzyl,

4-[(4'-(2-hydroxyethyl)piperazin- 1'-yl)C(O)O-]benzyl,

4-[(4'-phenylpiperazin- 1' -yl)C(O)O-]benzyl,

4-[(4'-(pyridin-2-y1)piperazin- 1'-yl)C(O)O-]benzyl,

4-[(4'-(4-trifluoromethylpyridin-2-y1)piper-1'-yl)C(O)O-]benzyl,

4-[(4'-(pyrimidin-2-y1)piperazin-1'-yl)C(O)O-]benzyl,

4-[(4'-acetylpiperazin- 1'-yl)C(O)O-]benzyl,

4-[(4'-(phenylC(O)-)piperazin- 1'-yl)C(O)O-]benzyl,

4-[(4'-(pyridin-4-ylC(O)-)piperazin- 1'-yl)C(O)O-]benzyl,

4-[(4'-(phenylNHC(O)-)piperazin-1'-yl)C(O)O-]benzyl,

4-[(4'-(phenylNHC(S)-)piperazin-1'-yl)C(O)O-]benzyl,

4-[(4'-methanesulfonylpiperazin- 1'-yl-C(O)O-]benzyl,

4-[(4'-trifluoromethanesulfonylpiperazin- 1'-yl-C(O)O-]benzyl,

4-[(morpholin-4'-yl)C(O)O-] benzyl,

3-nitro-4-[(morpholin-4'-y1)-C(O)O-] benzyl,

4-[(thiomorpholin-4'-yl)C(O)O-] benzyl,

4-[(thiomorpholin-4'-yl sulfone)-C(O)O-]benzyl,

4-[(pyrrolidin- 1'-yl)C(O)O-] benzyl,

4-[(2'-methylpyrrolidin-1'-yl)C(O)O-]benzyl,

4-[(2' -(methoxycarbonyl)pyrrolidin- 1'-yl)C(O)O-] benzyl,

4-[(2'-(hydroxymethyl)pyrrolidin-1'-yl)C(O)O-]benzyl,

4-[(2'-(N,N-dimethylamino)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2'-(N-methyl-N-toluene-4-sulfonylamino)ethyl)(CH_3)N-C(O)O-]benzyl,

4-[(2'-(morpholin-4'-yl)ethyl)(CH_3)NC(O)O-]benzyl,

4-[(2'-(hydroxy)ethyl)(CH_3)NC(O)O-] benzyl,

4-[bis(2'-(hydroxy)ethyl)NC(O)O-]benzyl,

4-[(2'-(formyloxy)ethyl)(CH_3)NC(O)O-]benyl,

4-[($CH_3OC(O)CH_2$)HNC(O)O-]benzyl,

4-[2'-(phenylNHC(O)O-)ethyl-]HNC(O)O-]benzyl,

3-chloro-4- [$(CH_3)_2$NC(O)O-]benzyl,

3-chloro-4-[(4'-methylpiperazin-1'-yl)C(O)O-] benzyl,

3-chloro-4-[(4'-(pyridin-2-y1)piperazin-1'-yl)C(O)O-]benzyl,

3-chloro-4-[(thiomorpholin-4'-yl)C(O)O-] benzyl and

3-fluoro-4-[$(CH_3)_2$NC(O)O-] benzyl .

Claim 44 (previously presented): A compound according to Claim 35 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy, 2-α-isopropyl-4-β-methylcyclohexoxy , 2-β-isopropyl-4-β-methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, -O$(CH_2CH_2O)_2CH_3$, 2-(phenoxy)ethoxy , -$OCH_2C(CH_3)_2$NHBoc, -NH_2, benzyloxy, -$NHCH_2COOH$, -$NHCH_2CH_2COOH$, -NH-adamantyl, -$NHSO_2$-*p*-CH_3-Φ, -$NHCH_{,2}CH_2COOCH_2CH_3$, -NHOY' where Y' is hydrogen, methyl, *iso*-propyl or benzyl, -O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, -OCH_2-$OC(O)C(CH_3)_3$, -$O(CH_2)_z$NHC(O)W where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR"C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R" is hydrogen or -$CH_2C(O)OCH_2CH_3$.

Claim 45 (previously presented): A compound selected from the group consisting of:

N-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*, *N*-dimethylcarbamyloxy)phenylalanine isopropyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*- dimethylcarbamyloxy) phenylalanine *tert*-butyl ester

N -(toluene-4-sulfonyl)sarcosyl-L-4-(*N*,*N*- dimethylcarbamyloxy) phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl

ester

N -(toluene-4-sulfonyl)sarcosyl-L-4-(isonipecotoyloxy) phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy) phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)-L-N-methylalanyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy) phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy) phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(l,1-dioxothiomorpholin-4-ylcarbonyloxy) phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(thiomorpholin-4-ylcarbonyloxy) phenylalanine

N-(toluene-4-sulfonyl)-L-N-methylalanyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-4-(l,1-dioxothiomorpholin-4-ylcarbonyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-N-methylalanyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

N-(toluene-4-sulfonyl)-L-*N*-methyl-2-(*tert*-butyl)glycinyl-L-4-(4-methylpiperazin-1-ylcarbonyloxy)phenylalanine *tert*-butyl ester

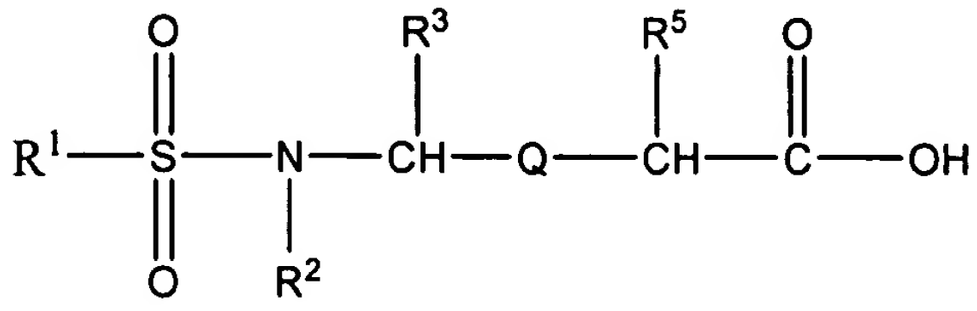
3-[*N*-(toluene-4-sulfonyl)-*N*-methylamino]-1-[1-carboxy-2-(*N, N*-dimethylcarbamyloxy) phenylethyl] azetidine

N-(toluene-4-sulfonyl)-L-prolyl-L-4-(isonipecotoyloxy) phenylalanine *tert*-butyl ester

N-(methanesulfonyl)-N-benzylglycinyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester, *tert*-butyl ester and neopentyl ester.

Claim 46 (previously presented): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I:



(I)

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted awl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2$-,

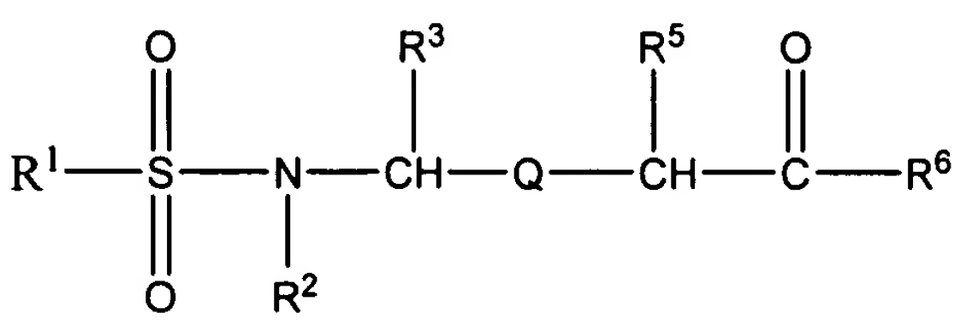
Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is -C(X)NR^7- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Claim 47 (previously presented): A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula IA:



(IA)

wherein

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^5 is -(CH2)x-Ar-R^5 and R$^{5'}$ is selected from the group consisting of -O-Z-NR^{8}R$^{8'}$ and -O-Z-R^{12} wherein R^8 and R$^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and R$^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -

C(O)- and -SO_2-,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, -$NH(CH_2)_pCOOY$ where *p* is an integer of from 1 to 8 and Y is as defined above, -$OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and -CH_2COOR^{11} where R^{11} is alkyl, and -$NHSO_2Z'$ where Z' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is -$C(X)NR^7$- wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof.

Claim 48 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

Claim 49 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein R^1 is selected from the group consisting of methyl, isopropyl, *n*-butyl, benzyl, phenethyl, phenyl, 4-methylphenyl, 4-*t*-butylphenyl, 2,4,6-trimethylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4- methoxyphenyl, 3,4-dimethoxyphenyl, 4-*t*-butoxyphenyl, 4-(3'-

dimethylamino-*n*-propoxy)- phenyl, 2-carboxyphenyl, 2-(methoxycarbonyl)phenyl, 4-($H_2NC(O)$-)phenyl, 4-($H_2NC(S)$-)phenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxyphenyl, 3,5-di-(trifluoromethyl)phenyl, 4-nitrophenyl, 4-aminophenyl, 4-($CH_3C(O)NH$-)phenyl, 4-(PhNHC(O)NH-)phenyl, 4-amidinophenyl, 4-($CH_3SC(=NH)$-)phenyl, 4-chloro-3-($H_2NS(O)_2$-)phenyl, 1- naphthyl, 2-naphthyl, pyridine-2-yl, pyridine-3-yl, pyrimidin-2-yl, quinolin-8-yl, 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl, morpholin-4-yl, 2-thienyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methylimidazol-4-yl, 1-N-methylpyrazol-3-yl, 1-N-methylpyrazol-4-yl, 1-N-butylpyrazol-4-yl, 1-N-methyl-5-chloropyrazol-4-y l, 1 -N-methyl-5-methyl-3 -chloropyrazol-4-yl , 2-thiazolyl and 5-methyl-1,3,4-thiadiazol-2-yl.

Claim 50 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-Φ.

Claim 51 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylmethyl, -CH_2CH_2- COOH, -CH_2-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH_2O-benzyl and hydroxymethyl.

Claim 52 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein Q is –C(O)NH- or –C(S)NH-.

Claim 53 (previously presented): A pharmaceutical composition according to Claims 46 or 47 wherein Ar is aryl or substituted aryl.

Claim 54 (previously presented): A pharmaceutical composition according to Claim 53 wherein Ar is phenyl or substituted phenyl and x is 1.

Claim 55 (previously presented): A pharmaceutical composition according to Claim 46 or 47 wherein R^5 is selected from the group consisting of

3-[$(CH_3)_2NC(O)O$-] benzyl,
4-[$(CH_3)_2NC(O)O$-] benzyl,
4-[$(CH_3)_2NS(O)_2O$-] benzyl,
4-[(piperidin-1'-yl)C(O)O-] benzyl,
4-[(piperidin-4'-yl)C(O)O-] benzyl,
4-[(1'-methylpiperidin-4'-yl)C(O)O-] benzyl,
4-[(4'-hydroxypiperidin-1'-yl)C(O)O-] benzyl,
4-[(4'-formyloxypiperidin- 1'-yl)C(O)O-] benzyl,
4-[(4'-ethoxycarbonylpiperidin- 1'-yl)C(O)O-] benzyl,
4-[(4'-carboxylpiperidin- 1'-yl)C(O)O-] benzyl,
4-[(3'-hydroxymethylpiperidin-1'-yl)C(O)O-] benzyl,
4-[(4'-hydroxymethylpiperidin-1'-yl)C(O)O-] benzyl,
4-[(4'-phenyl-1'-Boc-piperidin-4'-yl)-C(O)O-] benzyl,
4- [(4'-piperidon-1'-yl ethylene ketal)C(O)O-] benzyl,
4-[(piperazin-4'-yl)-C(O)O-] benzyl,
4-[(1'-Boc-piperazin-4'-yl)-C(O)O-] benzyl,
4-[(4'-methylpiperazin-1'-yl)C(O)O-] benzyl,
4-[(4' -methylhomopiperazin- 1' -yl) C(O)O-] benzyl,
4-[(4'-(2-hydroxyethyl)piperazin-1'-yl)C(O)O-] benzyl,
4-[(4'-phenylpiperazin-1'-yl)C(O)O-] benzyl,
4-[(4'-(pyridin-2-yl)piperazin- 1'-yl)C(O)O-] benzyl ,

4-[(4'-(4-trifluoromethylpyridin-2-y1)piperizan- 1'-yl)C(O)O-] benzyl,

4-[(4'-(pyrimidin-2-y1)piperazin-1'-yl)C(O)O-] benzyl,

4-[(4'-acetylpiperazin-1'-yl)C(O)O-] benzyl,

4-[(4'-(phenylC(O)-)piperazin-1'-yl)C(O)O-] benzyl,

4-[(4'-(pyridin-4-ylC(O)-)piperazin- 1'-yl)C(O)O-] benzyl,

4-[(4'-(phenylNHC(O)-)piperazin- 1' -yl)C(O)O-] benzyl ,

4-[(4'-(phenylNHC(S)-)piperazin- 1 '-yl)C(O)O-] benzyl,

4-[(4'-methanesulfonylpiperazin- 1'-yl-C(O)O-)benzyl,

4-[(4'-trifluoromethanesulfonylpiperazin- 1'-yl-C(O)O-)benzyl,

4-[(morpholin-4'-yl)C(O)O-] benzyl,

3-nitro-4-[(morpholin-4'-y1)-C(O)O-] benzyl,

4-[(thiomorpholin-4 '-yl)C(O)O-] benzyl ,

4-[(thiomorpholin-4'-yl sulfone)-C(O)O-] benzyl,

4-[(pyrrolidin-l' -yl)C(O)O-] benzyl ,

4-[(2'-methylpyrrolidin- 1'-yl)C(O)O-] benzyl,

4-[(2'-(methoxycarbonyl)pyrrolidin- 1'-yl)C(O)O-] benzyl,

4-[(2'-(hydroxymethyl)pyrrolidin- 1'-yl)C(O)O-] benzyl,

4-[(2'-(N,N-dimethylamino)ethyl)(CH_3)NC(O)O-] benzyl,

4-[(2 ' - (N-methyl-N-toluene-4-sulfonylamino)ethyl)(CH_3)N-C(O)O-]benzyl,

4-[(2'-(morpholin-4'-yl)ethyl)(CH_3)NC(O)O-] benzyl,

4-[(2'-(hydroxy)ethyl)(CH_3)NC(O)O-] benzyl,

4-[bis(2'-(hydroxy)ethyl)NC(O)O-] benzyl,

4-[(2'-(formyloxy)ethyl)(CH_3)NC(O)O-] benzyl,

4-[($CH_3OC(O)CH_2$)HNC(O)O-] benzyl,

4-[2'-(phenylNHC(O)O-)ethyl-]HNC(O)O-] benzyl,

3-chloro-4-[($(CH_3)_2$NC(O)O-] benzyl,

3-chloro-4-[(4 '-methylpiperazin-1'-yl)C(O)O-] benzyl,

3-chloro-4-[(4'-(pyridin-2-yl)piperazin-1'-yl)C(O)O-] benzyl,
3 -chloro-4- [(thiomorpholin-4'-yl)C(O)O-] benzyl, and
3-fluoro-4-[$(CH_3)_2NC(O)O$-] benzyl.

Claim 56 (previously presented): A pharmaceutical composition according to Claim 47 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, cyclopropylmethoxy, neopentoxy , 2-α-isopropyl-4-β-methylcyclohexoxy, 2- β-isopropyl-4-β -methylcyclohexoxy, 2-methoxyphenoxy, 2-(morpholin-4-yl)ethoxy, $-O(CH_2CH_2O)_2CH_3$, 2-(phenoxy)ethoxy, $-OCH_2C(CH_3)_2NHBoc$, $-NH_2$, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHSO_2$-*p*-CH_3-Φ, $-NHCH_2CH_2COOCH_2CH_3$, -NHOY' where Y' is hydrogen, methyl, *iso*-propyl or benzyl, -O-(N-succinimidyl), -O-cholest-5-en-3- β-yl, $-OCH_2$-$OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where z is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR"C(O)-R' where R' is aryl, heteroaryl or heterocyclic and R" is hydrogen or $–CH_2Z(O)OCH_2CH_3$.

Claim 57 (previously presented): A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claim 1 or 35 under conditions wherein said compound binds to VLA-4.

Claim 58 (previously presented): A method for treating an inflammatory condition in a mammalian patient which condition is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of a pharmaceutical composition of Claim 46 or 47.

Claim 59 (previously presented): The method according to Claim 58 wherein said inflammatory condition is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury.